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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/436,164	REUBINOFF ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-26,38-44 and 47-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-26,38-44 and 47-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on January 20, 2004 has been entered.

DETAILED ACTION

This application is an original application filed November 9, 1999 which claims benefit of foreign applications PP7009, filed November 9, 1998, and PQ2852, filed September 15, 1999, both filed in Australia.

Applicants' amendment filed January 200, 2004 has been received and entered. Claims 1-19, 27-37, 45, 46, have been canceled. Claims 47-55 have been added. Claims 20-26, 38-44 and 47-55 are pending and currently under examination.

Election/Restriction

Applicant's election with traverse of groups II in Paper No. 10 was acknowledged. Applicants have not provided any new grounds of traversal and have canceled claims which were drawn to remaining inventions restricted to the remaining groups. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-26, 38-44 and 47-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically,

Claim 20 is unclear in the recitation of "said conditions" recited in the second to last line, because the prior steps provide for various specific conditions, growing the embryo, culturing ICM cells and culturing stem cells. The antecedent basis for "said conditions" is not clear because an embryo ant the ICM cells comprise stem cells, in addition to an isolated source of stem cells. In addition, the claim is unclear because the preamble indicates that the method is "of inducing somatic differentiation" of stem cells, however the final step teaches that the conditions should not permit stem cell renewal or death "or induce their differentiation into extraembryonic lineages" and a differentiated somatic cell would considered an extraembryonic lineage. Further, the final step requires that said method comprises conditions "that induce somatic differentiation" however it is unclear how this is accomplished if the conditions used do not permit differentiation into extraembryonic lineages.

Claim 47 is unclear because the preamble indicates that the method is "of inducing somatic differentiation" of stem cells, however the final step teaches that the conditions should not permit stem cell renewal or death "or induce their differentiation into extraembryonic lineages" and a differentiated somatic cell would considered an extraembryonic lineage.

In both cases above, dependent claims are included in the basis of the rejection because they fail to further define the specific conditions that are being used or comprised by the claims. The fibroblast cells used as a feeder layer may be tested, however what is being assayed is not clearly set forth. Specific markers of stem cells are taught, however there is no teaching of cell markers of differentiated cells or an intermediate cell type between a stem cell and differentiated cell, where even if one would test the fibroblast cells it is unclear what would be assessed where the conditions do not allow for stem cell renewal but do not allow for extraembryonic lineages.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 20-26, 38-44 stand rejected and claims 47-55 are rejected under 35 U.S.C. 102(b) as being anticipate by Thomson *et al.* (Science 282:1145-1147).

Claims 20-26, 38-44 stand rejected and claims 47-55 are rejected under 35 U.S.C. 102(e) as being anticipate by Thomson (US Patent 6,200,806).

The newly added claims are noted, however though an active method step to providing a somatic differentiation-inducing fibroblast feeder layer has been recited, as discussed above in the basis of the rejection made under 35 USC 112, second paragraph, the metes and bounds of

this cell type and its properties is unclear. Further, as discussed previously, the language used in the instant claims is open and comprises the use of any fibroblast cell line because the conditions for differentiation or stem cell maintenance may be provided by properties besides the cells such as the media or the specific way of culturing (i.e. prolonged time in culture).

The claims recite a "method of inducing somatic differentiation" and can reasonably interpreted as an embryonic cell, or alternatively as a fully differentiated cell. Thomson *et al.* teach human pluripotent embryonic cell lines. Thomson *et al.* teach three cell lines: H13 and H14 which have a normal XY karyotype and H7 which has a normal XX karyotype (page 1145; second column). Thomson *et al.* teach that when the cell lines are injected into an immunodeficient mouse the cell lines can differentiate into endoderm, mesoderm and ectoderm cell types (page 1146; middle of first column and page 1147; figure 4). Further, characterization of the lines in culture, differentiation of the cells results in various cell types, including neuronal cells (neural epithelium shown in figure 4B). In characterizing the stem cell lines, various culturing methods were used to differentiate the cell lines. Among the parameters taught to affect differentiation of the cell lines was the feeder layer, the cell density, and various growth factors. In view of the breadth and lack of clarity of the claimed methodology the methods and general teachings of Thomosn *et al.* describing methods to stimulate or allowing the cell lines to differentiate in culture, anticipate the methods set forth in the instant claims.

With respect to '806, Thomson teaches a purified preparation of pluripotent human embryonic stem cells which are capable of differentiating into derivatives of the endoderm, mesoderm and ectoderm. Again, in the characterization of the cells it is demonstrated that the cells can differentiate into neural cells (column 11; lines 31-32). Further, conditions to culture

the cells in gelatin treated culture plates is taught when placed in culture and allowed to grow for two weeks after achieving confluence, or grown without a fibroblast feeder layer the cells spontaneously differentiate (description in paragraphs bridging columns 14-15 and in Figure 6). Thus, the differentiated human cells and methods to differentiate said cells from pluripotent embryonic cells taught in Thomson *et al.* anticipate the claims.

Applicants have summarized the teaching of both the references by Thomson noting that Thomson *et al.* only teach spontaneous differentiation not the specific induction of differentiation, and that they do not appreciate the specific properties that a fibroblast cell line may possess and may have on a stem cell when cultured on a particular feeder layer. Applicants argue that the specification provides culture conditions which induce differentiation and that these conditions are recited in the claims. Applicants argue that the present inventor uniquely recognized that various batches of fibroblast cells differed in their potential to support ES cell growth and differentiation in culture. Applicants' arguments have been fully considered, but not found persuasive.

As noted in the previous office action and in the advisory action, the instant claims encompass the conditions for the spontaneous differentiation of ES cells taught by Thomson *et al.* In particular, the claims are vague and broadly encompass almost any culturing condition. Importantly, the instant specification teaches that a variety of conditions can be used to induce differentiation including "cultivating to a high density in monolayer" (page 22, lines 6-8) which is the same condition inducing differentiation in Thomson *et al.* Further, Examiner notes that the specification teaches that conditions such as period in culture, density and feeder layer can affect

deafferentation of the cells in culture (page 20), however Thomson *et al.* also teaches that time between passage and density are important factors in culturing ES cells, in particular with respect to their affect on differentiating the ES cells in culture. With respect to the role of the fibroblast feeder cell layer, clearly Thomson *et al.* teach that a fibroblast feeder layer is required to prevent differentiation of human ES cells. Further, Thomson *et al.* teaches that under the appropriate conditions ES cells can be induced to differentiate on a fibroblast feeder layer. The present claims are broad encompassing the methods of maintaining and differentiating ES cells taught by Thomson *et al.* It may be, as Applicants argue, that various specific fibroblast cells lines provide a more or less favorable substrate to maintain embryonic stem cells, however the instant claims are very broad and even dependent claims are not restricted to any particular fibroblast cell line or that the fibroblast feeder cells provide any specific differentiation affect. Further, while the handling or the source of fibroblast cell may affect its suitability to serve as a feeder layer, there is no objective evidence of record that the fibroblast layer itself uniquely affects ES cells differentiation, and that other conditions such as growth at high density or the addition of differentiation factors to the media are required for differentiation. It is noted that Applicants describe two different feeder cell lines, B-83 and B-72 (amendment, pages 7-8), however these are not presented in the specification nor is there any specific data to evaluate the nature of these cells or the conditions of culture which provided the affect described in Applicants' comments. The instant claims encompass any culturing condition which induce any type of differentiation of the ES cells. Thomson *et al.* teach the same method of isolating embryonic stem cells as recited in the claims and provide specific conditions in which the ES cells differentiated in culture.

Given the breadth of the instant claims, the teaching of Thomson *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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